

REMARKS/ARGUMENTS

In response to the Office Action of December 3, 2003, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claims 1, 39, 40 and 44-46 have been amended. Claims 2-38 were cancelled in a previous response (filed on September 22, 2003). Claims 1 and 39-46 remain pending in the instant application and are currently under examination.

No new matter has been added by the amendments to the specification made herein.

In the "Background of the Invention" section a punctuation error was corrected at page 1, line 23.

The description of the reference at page 5 has been amended to correct a typographical error in the international application number. The corresponding international publication number has also been added.

The "Description of the Figures" section has been amended to add sequence identification numbers and to clearly indicate that Figures 2 and 3 show the mass spectrum profiles of the disclosed biopolymer markers.

Several protocols at pages 41-45 have been amended to properly identify trademark names (TRITON, TRIS and EPPENDORF). The protocol titles at page 41 (lines 6 and 20), page 42 (line 12) and page 43 (lines 3 and 16) were underlined in the original disclosure and do not indicate text amended herein.

The paragraph at page 46 was amended for consistency of language and to correct typographical errors.

In the "Detailed Description" section, the term "cerebrospinal fluid" has been added to define the abbreviation "CSF" at page 49, line 9 in order to provide additional support for cerebrospinal fluid as recited in claim 41. "CSF" is a well known abbreviation for cerebrospinal fluid in the biochemical art. Kits for determining the presence of the claimed biopolymer markers are discussed at page 47, lines 7-23; cerebrospinal fluid is noted to be one type of sample which can be used in the discussed kits. A typographical error within the same paragraph at page 49 has also been amended (skill replaced skilled).

No new matter has been added by the amendments to the claims made herein.

Claim 1 has been amended to explicitly claim the biopolymer marker (SEQ ID NO:1). The term "biopolymer marker" is used throughout the specification as originally filed, see, for example, page 1, line 8.

Claim 39 has been amended to clearly disclose the relationship between the presence of the claimed biopolymer marker (SEQ ID NO:1) and insulin resistance. Claim 39 has also been amended to explicitly indicate how the presence of the claimed biopolymer marker is determined from mass spectrum profiles. The changes to claim 39 find basis throughout the specification as originally filed, see, for example, page 35, lines 14-18, page 46, lines 4-11 and Figures 1 and 2.

Claim 44 has been amended to correspond with the biopolymer marker of claim 1 (as amended herein). Support for various types of kits can be found in the original disclosure, see for example, page 36, lines 9-12 and page 47, line 7 to page 48, line 16.

Claims 45 and 46 have been amended to provide proper antecedent basis for the term "kit" in claim 44 (as amended herein).

Rejections under 35 USC 112, first paragraph

Claims 1 and 39-46, as presented on September 22, 2003, stand rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the written description requirement. The claims contain subject matter which was allegedly not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time that the

application was filed, had possession of the claimed invention.

The Examiner alleges that there is no support in the specification for a biopolymer marker peptide consisting of amino acid residues 2-12 of SEQ ID NO:1. The Examiner invites Applicants to show support or cancel the new matter.

Applicants respectfully disagree with the Examiner's position. At page 46 of the specification as originally filed the amino acid sequence of SEQ ID NO:1 is disclosed as (K)LVPFATELHER(L). The amino acid sequence of SEQ ID NO:1 is also disclosed in the same manner in the claims as originally filed. The first amino acid residue (K) and the last amino acid residue (L) are clearly shown separated from the second and twelfth amino acid residues. When one of skill in the art sequences peptides, predicted residues are often shown enclosed in parentheses to separate the predicted residues from identified residues. One of skill in mass spectrometric techniques would be familiar with this practice. Applicants do not claim any new residues, i.e. residues which were not originally disclosed; residues 2-12 are simply a fragment of the originally presented 13 amino acid peptide, SEQ ID NO:1. Thus, contrary to the Examiner's assertion, the specification as originally filed provides support for a biopolymer marker consisting of amino acid residues 2-12 of SEQ ID NO:1.

However, in the interest of compact, efficient prosecution,

Applicants have amended the claims to remove the phrase "amino acid residues 2-12".

Accordingly, since the pending claims are now drawn to a biopolymer marker consisting of SEQ ID NO:1, Applicants respectfully request that the rejection under 35 USC 112, first paragraph (written description) be withdrawn.

Claims 1 and 39-46, as presented on September 22, 2003, stand rejected under 35 USC 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner asserts that the claims are directed to a biopolymer marker peptide consisting of SEQ ID NO:1 diagnostic for insulin resistance, methods of using and a kit and the specification does not enable one of skill in the art to make and use the biopolymer marker peptide.

Applicants respectfully disagree with the Examiner's position.

Although Applicants believe that the instant specification, as originally filed, fully supports the claim that an isolated peptide consisting of SEQ ID NO:1 is diagnostic for insulin resistance, in the interest of compact, efficient prosecution,

Applicants have removed the term "diagnostic" from the claims and note that the isolated peptide consisting of SEQ ID NO:1 is linked to insulin resistance.

According to the web site dictionary.com the term "linked" refers to the condition of being associated with or connected to (see attached document as accessed from the internet; reference 1). The instant specification fully supports a connection and/or an association of the claimed peptide with insulin resistance. The instant specification states at page 35, lines 14-18 that an objective of the invention is to evaluate samples containing a plurality of biopolymers for the presence of disease specific biopolymer marker sequences which evidence a link to at least one specific disease state.

The Examiner maintains that applicant has not shown how to use SEQ ID NO:1 and that the specification does not enable one of ordinary skill in the art to correlate SEQ ID NO:1 with insulin resistance.

Applicants respectfully disagree with the Examiner's assertions.

The "test of enablement" is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the prior art without undue experimentation (see MPEP 2164.01).

Furthermore, the decision in *In re Brandstadter* (179 USPQ 286; MPEP 2164.05) has established that the evidence provided by applicant (to overcome an enablement rejection) need not be conclusive but merely convincing to one of skill in the art.

Applicants respectfully submit that the instant specification provides sufficient evidence to convince one of skill in the art that the claimed peptide (SEQ ID NO:1) is linked and/or associated with insulin resistance.

Claim 1 has been amended to specifically recite an isolated peptide consisting of SEQ ID NO:1, a peptide which the instant specification identifies as related to insulin resistance. Claim 1, as amended herein, does not recite that the claimed isolated peptide is diagnostic for insulin resistance, nor does it recite that the claimed isolated peptide is related to insulin resistance, even though Applicants believe that the specification, as originally filed, fully supports both of these recitations. Furthermore, the phrase "consisting of" is closed language and excludes any element, step or ingredient not specified in the claims (see MPEP 2111.03). Thus, the scope of claim 1 is limited to this specific peptide.

The Examiner repeatedly asserts that the data provided in Figure 1 is ambiguous. The Examiner further asserts that the drawings do not correlate SEQ ID NO:1 to insulin resistance and

that the specification fails to provide any clear guidance in Figure 1 distinguishing insulin resistance as a marker to the presence of the marker in healthy patients, i.e, there is the presence of the marker in healthy patients and also the presence of the marker in one patient with insulin resistance and absent in the other patient with insulin resistance.

Applicants respectfully disagree with the Examiner's interpretation of Figure 1.

The proteins shown in the gel of Figure 1 were resolved from patient samples using the preparatory protocol, HiQ 1 Elution column chromatography (step by step protocol at page 43 of the instant specification). The 10 lanes of the gel are clearly labeled (from the left); Lane 1 contains low molecular weight standards necessary to interpret the results of the separation; Lane 2 contains a sample obtained from a patient with a history of Type I diabetes; Lanes 3 and 4 each contain a sample obtained from a patient with a history of insulin resistance, Lanes 5 and 6 each contain a sample obtained from a patient with a history of Type II diabetes; Lanes 7-9 each contain a sample obtained from a patient determined to be normal with regard to insulin resistance and diabetes; and Lane 10 contains high molecular weight standards necessary to interpret the results of the separation. One of skill in the art would compare expression between the disease and normal

states and select bands which are differentially expressed between the two states for further characterization (see page 38, lines 7-11 of the instant specification) since peptides which are differentially expressed between a disease state and a normal state are considered potential markers for the disease condition.

At page 46, lines 4-11 of the instant specification as originally filed, SEQ ID NO:1 is identified as apolipoprotein A-IV precursor protein having a molecular weight of about 1312 daltons. The description of Figure 2 at page 37 of the instant specification as originally filed indicates that the mass spectrum profile depicted in the figure is that of ion 1312; SEQ ID NO:1. In Figure 1, there is a Band #7 present in a sample resolved from a patient determined to be normal with regard to insulin resistance and diabetes. This Band #7 has a label "apolipoprotein A-IV precursor" indicating that this protein, i.e. the claimed marker, was resolved from this sample (normal, Lane 9). Thus, contrary to the Examiner's assertion, it is clear that the claimed SEQ ID NO:1 corresponds to Band #7 as shown in Figure 1.

Band #7 appears to show strong expression in a sample obtained from a patient determined to be normal with regard to insulin resistance and diabetes (Lane 9). Expression of Band #7 also appears in Lanes 7 and 8, each of which contain samples obtained from patients determined to be normal with regard to insulin

resistance and diabetes.. Band #7 also appears to show expression in a sample obtained from a patient having a history of insulin resistance (Lane 3). Band #7 does not appear to show expression in a sample obtained from a patient with a history of insulin resistance (Lane 4) and in samples obtained from 3 patients having histories of diabetes (Lanes 2, 5 and 6). Thus, contrary to the Examiner's assertions, Figure 1 correlates SEQ ID NO:1 with insulin resistance, therefore the data shown in Figure 1 is not ambiguous.

Peptides which are differentially expressed between a disease state and a normal physiological state are often determined to be associated with the disease state. The claimed biopolymer marker peptide (SEQ ID NO:1) is identified in all of the normal samples and in one disease sample and, likewise is absent in four disease samples; thus, the instant inventors link the claimed biopolymer marker peptide with insulin resistance.

Additionally, Applicants respectfully submit that such protocols are common practice in the field of proteomics. For example, Scott D. Patterson presents the state of the art in mass spectrometry/proteomics by summarizing the Asilomar Conference on Mass Spectrometry (see attached article, Physiological Genomics 2:59-65 2000; reference 2). This conference took place in 2000, thus coinciding with the time that the instant inventors were working to develop the instant invention.

In the disclosed method of the instant invention, proteins (as seen on a gel) that are identified as differentially expressed between a disease and a non-disease state are selected for excision (from the gel) and identification (see, for example, page 38, lines 7-11 of the instant specification as originally filed, and Figure 1). Such selection methods are common practice in the search for biomarkers of specific physiological states. For example, at page 61, right column of Patterson, several automation processes are discussed in the section titled "Automated identification of gel-separated proteins by mass spectrometry". This discussion begins with the following statement:

"Following quantitative analysis of 2-DE patterns, the next step is the identification of all protein spots that display differential expression."

Thus, it is concluded that it is common practice to select potential disease markers by their differential expression between a disease and a non-disease state.

Furthermore, Applicants respectfully submit that many of the methods disclosed in the instant specification are routinely practiced by those of ordinary skill in the art attempting to identify biomarkers of particular physiological states.

For example, at page 64, left column of Patterson is a description of the SELDI approach (as discussed at the conference

by Scot Weinberger) wherein defined chemical/biochemical surfaces are utilized to allow fractionation of proteins from biological fluids in a reproducible manner. This reproducibility allows comparisons between different samples to be made. Weinberger described a search for markers of benign prostate hyperplasia that, like prostate cancer, displays elevated prostate specific antigen (PSA) levels. The fraction exhibiting a difference between these samples was able to be enzymatically digested, and a number of peptides were generated. These peptides were able to be fragmented using the MALDI-Qq-TOF (a procedure described by Ken Standing at the conference, page 62, left column of Patterson). It was found that there appears to be a difference in the relative level of seminogelin fragments between these two states (prostate cancer and benign prostatic hyperplasia), thus providing a potential differential marker.

Applicants respectfully draw the Examiner's attention to the fact that the method described by Weinberger is analogous to the method described in the instant specification. Furthermore, when interpreting data Weinberger uses the same approach to interpretation as the instant inventors in order to identify seminogelin fragments as a potential marker to distinguish between benign prostate hyperplasia and prostate cancer based on differential expression of the fragments. Additionally, Applicants

respectfully point out to the Examiner that Weinberger linked differential expression of seminogelin to benign prostate hyperplasia and prostate cancer without analysis of a sample from a control patient free of disease or analysis of a sample from a patient having another disease, which is not benign prostate hyperplasia or prostate cancer. Such linking of markers with disease through differential expression is commonly practiced in proteomics.

Furthermore, Applicants assert that those of skill in the art are both highly knowledgeable and skilled and it is obvious that no undue experimentation would be required for a skilled artisan to follow any of the electrophoretic, chromatographic and mass spectrometric protocols presented in the instant specification in order to use the claimed invention. One of skill in the art would be able to view a gel, such as that shown in Figure 1 from which the claimed peptide was identified (SEQ ID NO:1), and recognize a difference between two comparable samples (disease state vs. non-disease state) and further recognize that the peptides present within the gel are differentially expressed between the two sample types.

The data presented in the figures, derived from the working examples established at the time of filing, discloses that the claimed peptide (SEQ ID NO:1) is differentially expressed between

insulin resistance and a normal physiological state, thus it can be reasonably predicted that such peptide is linked to insulin resistance. Furthermore, the figures identify SEQ ID NO:1 and the specification discloses how such a sequence was identified as a notable sequence in relation to insulin resistance.

Thus, Applicants contend a skilled practitioner would find that the data presented in the instant specification is convincing with regard to a link between the claimed biopolymer marker peptide (SEQ ID NO:1) and insulin resistance. Therefore, Applicants respectfully submit that the claimed invention satisfies the precedent as set forth in *In re Brandstadter*.

Considering the above comments, it is clear that both the specification and the prior art disclose how to make and use the instant invention. Accordingly, Applicants respectfully contend that the instant invention satisfies the "test for enablement" since one skilled in the art could make or use the invention from the disclosures in the specification coupled with information known in the prior art without undue experimentation.

The Examiner states that Applicants' argument that Figure 1 indicates that samples were taken from 5 patients that exhibited disease states and compared with samples from healthy patients is not found persuasive because there is no support in the specification. On page 31 of the specification, applicant asserts

that samples may be taken from a patient at one point in time, as a single sample or as multiple samples or at different points in time such that analysis is carried out on multiple samples for ongoing analysis. The specification further recites that a sample is taken from a patient that may have possible symptoms of a disease and is analyzed. After 3-6 months from the first sample taken, another one may be taken and analyzed to diagnose or monitor a disease state and Figure 1 does not explain the data.

Applicants respectfully submit that the Examiner's interpretation of Figure 1 is incorrect.

Lanes 2-6 of the gel shown in Figure 1 are clearly labeled with a disease state; Type I diabetes, insulin resistance and Type II diabetes and Lanes 7-9 are clearly labeled normal. Thus, 5 samples obtained from patients that exhibited disease states (Lanes 2-6) and samples obtained from patients determined to be normal (Lanes 7-9) are clearly compared in the gel.

Accordingly, Applicants respectfully submit that the Examiner has no basis for the assertion that there is no support in the specification that Figure 1 indicates that samples were taken from 5 patients that exhibited disease states and compared with samples from healthy patients when such a sample comparison is seen in Figure 1 of the instant specification as originally filed.

Furthermore, at page 31 of the instant specification as

originally filed, taking single and/or multiple samples at different points in time is disclosed as a further contemplated embodiment of the invention and is not intended to be construed as the only embodiment. The information disclosed at page 31 is not required to interpret the data shown in Figure 1. When one of ordinary skill in the art views the gel as shown in Figure 1, one would recognize a comparison of protein expression in a disease state (insulin resistance or diabetes) and a normal physiological state. Thus, contrary to the Examiner's assertion, the data of Figure 1 is explained.

The Examiner asserts that the declaration under 37 CFR 1.132 filed on September 22, 2003 is insufficient to overcome the rejection of claims 1, and 39-46 based upon the 112 first rejection as set forth in the last Office Action because: Applicant's declaration was not found persuasive because the data in Figure 1 is ambiguous. The normal patient exhibited a strong presence of the marker while the other two normal patients exhibited a weak presence of the marker. The diseased patient exhibited also a weak presence for insulin resistance making it hard to distinguish if the biomarker is indicative of insulin resistance.

Applicants respectfully disagree with the Examiner's assertion.

It has already been established in the paragraphs above that

the data in Figure 1 is not ambiguous. The Declaration under 37 CFR 1.132 filed on September 22, 2003 was submitted to clarify the use of controls in the experiments described in the instant specification and to further indicate how bands were selected from the gels for excision and sequencing.

The Examiner asserts that the prior art of record fails to disclose a biopolymer marker peptide for insulin resistance, method and kit consisting of SEQ ID NO:1, and additionally asserts that there is no predictability that SEQ ID NO:1 is diagnostic of insulin resistance.

Apparently, the Examiner believes that the lack of disclosure in the prior art with regard to SEQ ID NO:1 as a marker of insulin resistance precludes SEQ ID NO:1 from being a marker of insulin resistance.

It has been established that the mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it (see MPEP 2164.02).

Thus, Applicants respectfully submit that the Examiner's assertion regarding the lack of disclosure/predictability in the prior art is insufficient to support a rejection of the currently pending claims under 35 USC 112, first paragraph (enablement).

The guidelines for a "test of enablement" indicate that if a

statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 USC 112, is satisfied (see MPEP 2164.01(c)).

Although the prior art does not specifically recognize that the claimed marker consisting of SEQ ID NO:1, a fragment of the apolipoprotein A-IV precursor protein, is related to insulin resistance, it does recognize that the plasma lipid profile is modified in insulin resistance and diabetes (see attached abstract of Rigoli et al. Acta Diabetol 32(4):251-256 1995; reference 3). Furthermore, it is known that ApoA-IV genetic polymorphism is associated with myocardial infarction in obese non-insulin dependent (Type II) diabetes patients (see attached abstract of Rewers et al. Diabetes 43(12):1485-1489 1994; reference 4). Thus, the level and/or function of apolipoprotein A-IV is potentially altered in insulin resistance. When one of skill in the art observes differential expression of the claimed biopolymer marker peptide between insulin resistance patients and patients determined to be normal with regard to insulin resistance; one of skill in the art will connect this peptide with potential diagnostics and/or therapeutics for insulin resistance (see above discussion of the Patterson reference).

Thus, Applicants respectfully submit that since the

specification demonstrates a link between the claimed peptide (SEQ ID NO:1) and insulin resistance and that this link connotes the use of the claimed peptide in potential diagnostics and/or therapeutics of insulin resistance, the requirement of "how to use" under 35 USC 112, first paragraph is satisfied.

Furthermore, Applicants respectfully submit that one of ordinary skill in the art would find the suggestion of a link between the claimed peptide (SEQ ID NO:1) and insulin resistance to be reasonable.

At page 46, of the specification as originally filed, SEQ ID NO:1 is identified as a fragment of apolipoprotein A-IV precursor protein. As mentioned above, the plasma lipid profile is modified in insulin resistance (see reference 3). Additionally, genetic polymorphisms in the ApoA-IV gene could cause alterations in the function of the ApoA-IV protein that in turn, can influence a disease state (see reference 4). One of ordinary skill in the art, considering the known involvement of apolipoprotein A-IV with insulin resistance, upon observation of the differential expression of SEQ ID NO:1 in insulin resistance versus normal control, would find it reasonable to believe that this peptide is related and/or linked to insulin resistance.

Therefore, one of ordinary skill in the art would recognize the linkage between SEQ ID NO:1, apolipoprotein A-IV and insulin

resistance and thus would also find the suggestion of SEQ ID NO:1 as a marker for insulin resistance entirely reasonable.

The Examiner cites an article; Tockman et al. (see attached abstract, Cancer Research 52(9 suppl):2711s-2718s 1992; reference 5) which is allegedly relevant to the instant invention.

According to the Examiner, the article of Tockman et al. is analogous to the instant invention since both are drawn to biopolymer research indicative of a disease state. Tockman et al is deemed to teach conditions necessary for a suspected cancer biomarker (intermediate end point marker) to have efficacy and success in a clinical application. The reference is drawn to biomarkers for early lung cancer detection, however the basic principles are applicable to other oncogenic disorders, according to the Examiner. Tockman et al is deemed to teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials. Early stage markers of carcinogenesis have clear biological plausibility as markers of pre-clinical cancer if validated to a known cancer outcome. According to the Examiner, Tockman et al reiterates that the predictability of the art in regards to cancer prognosis and the estimation of life experience within a population

with a disease or disorder are highly speculative and unpredictable.

Tockman et al is deemed to teach that the essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical disease and link those marker results with histological confirmation of disease.

Applicants respectfully disagree with the Examiner's reliance on the article by Tockman et al.

The Tockman et al article is concerned with early detection of lung cancer biomarkers and apparently does not discuss biomarkers for insulin resistance or diabetes.

Tockman et al. link several biopolymer markers to lung cancer in a manner analogous to that of the instant specification. Tockman et al. state at page 2712s, left column:

"A functional membrane-associated bombesin receptor recently has been isolated from human small cell lung carcinoma (NCI-H345) cells (23), and bombesin-like peptides have been found in the bronchial lavage fluid of asymptomatic cigarette smokers (24). Thus markers of growth factor expression, insofar as they reflect oncogene activation, may also hold promise for the detection of early (preneoplastic) lung cancer."

From this statement, it is clearly evident that Tockman et al.

link bombesin with small cell lung cancer and associate it with potential diagnostics for small cell lung cancer. It does not appear that bombesin was "validated" and/or subjected to any "criteria" prior to this association.

Additionally, Tockman et al. state at page 2713s, left column:

"Evidence of a transformed genome, by expression of tumor-associated antigens, oncofetal growth factors, or specific chromosomal deletions has clear biological plausibility as a marker of preclinical lung cancer."

From this statement, it appears that Tockman et al. believe that the expression of certain proteins provides evidence of a transformed genome and since this transformed genome is associated with lung cancer, it is reasonable to believe that these certain proteins are potential markers.

Such parallel reasoning between Tockman et al. and the instant specification, further supports Applicants contention that one of ordinary skill in the art would not have any difficulty seeing a link between the claimed biopolymer marker peptide (SEQ ID NO:1) and insulin resistance.

It is noted that in chemical and biotechnical applications, evidence actually submitted to the FDA to obtain approval for clinical trials may be submitted to support enablement of an invention. However, considerations made by the FDA for approving

clinical trials are different from those made by the PTO in determining whether a claim is enabled (see *Scott v. Finney* 32 USPQ 2d 1115 and MPEP 2164.05)

The Examiner is reminded that the considerations made by the PTO involving clinical trials are less stringent than the considerations made by the FDA. Evidence presented by applicant to provide enablement of an invention need only be convincing to one of skill in the art and not conclusive. Thus, Applicants respectfully submit that compliance with the "criteria" of Tockman et al. is not necessary in order to show that the instant invention is enabled.

In conclusion, Applicants respectfully submit that they have shown how to correlate the claimed biopolymer marker (SEQ ID NO:1) with insulin resistance and thus have also demonstrated how to use the claimed biopolymer marker (SEQ ID NO:1). Applicants claim that the differential expression of SEQ ID NO:1 between insulin resistance patients and patients determined to be normal with regard to insulin resistance evidences a link between the claimed peptide (SEQ ID NO:1) and insulin resistance; a statement which is enabled by the instant specification, as evidenced by the arguments presented herein. Applicants assert that one of ordinary skill in the art when reviewing the instant specification, given the level of knowledge and skill in the art, would recognize the link between

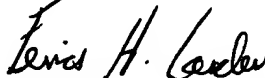
Appl. No. 09/993,366 Amdt. dated Reply to Office action of December 3, 2003

the claimed biopolymer marker (SEQ ID NO:1) and insulin resistance and would further recognize how to use the claimed peptide (SEQ ID NO:1) as a marker for insulin resistance. Thus, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendments to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,



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